

Exhibit 14

Effects of risk factors for ovarian cancer in women with and without endometriosis

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Objective: To evaluate the associations between 10 well-established ovarian cancer risk factors and risk of ovarian cancer among women with vs. without endometriosis.

Design: Pooled analysis of 9 case-control studies in the Ovarian Cancer Association Consortium.

Setting: Population-based.

Patient(s): We included 8,500 women with ovarian cancer, 13,592 control women.

Intervention(s): Ten well-established ovarian cancer risk factors.

Main Outcome Measure(s): Risk of ovarian cancer for women with and without endometriosis.

Result(s): Most risk factor-ovarian cancer associations were similar when comparing women with and without endometriosis, and no interactions were statistically significant. However, body mass index (BMI) 25–<30 kg/m² was associated with increased ovarian cancer risk among women with endometriosis (odds ratio [OR] = 1.27, 95% confidence interval [CI] 1.00–1.60), but not associated with the risk among women without endometriosis (OR = 0.97; 95% CI, 0.91–1.05) when compared with BMI 18.5–<25 kg/m²; an increased risk was observed for a BMI ≥ 30 kg/m², although there was little difference comparing women with endometriosis (OR = 1.21; 95% CI, 0.94–1.57) to women without (OR = 1.13; 95% CI, 1.04–1.22) (*P*-interaction = .51). Genital talcum powder use and long-term menopausal estrogen-only therapy use showed increased ovarian cancer risk, but risk appeared greater for those with endometriosis vs. those without (genital talcum powder: OR = 1.38; 95% CI, 1.04–1.84 vs. OR = 1.12; 95% CI, 1.01–1.25, respectively; ≥ 10 years of estrogen-only therapy: OR = 1.88; 95% CI, 1.09–3.24 vs. OR = 1.42; 95% CI, 1.14–1.76, respectively); neither of these interactions were statistically significant (*P*-interaction = .65 and *P*-interaction = .96, respectively).

Conclusion(s): The associations between ovarian cancer and most risk factors were similar among women with and without endometriosis. However, there was some suggestion of differences by endometriosis status for BMI, menopausal hormone therapy use, and genital talcum powder use, highlighting the complexity of ovarian cancer etiology. (Fertil Steril® 2022; ■:■–■. ©2022 by American Society for Reproductive Medicine.)

Key Words: Endometriosis, ovarian cancer, effect modification, risk factors, interactions



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Endometriosis is a common gynecologic condition that involves the growth of endometrial glands and stroma outside the uterine cavity (1). Its association with the risk of ovarian cancer is well established; there is a 3-fold increased risk for the clear cell histotype and a 2-fold increased risk for the endometrioid as well as low-grade serous histotypes (1, 2). In general, endometriosis and ovarian cancer are thought to have a shared pathophysiology (3), and there is also some evidence of a genetic link between these conditions (4, 5).

It has been suggested that the effects of ovarian cancer risk factors may be different among women with vs. without endometriosis. An Australian record-linkage study by Dixon-Suen et al. (6) and a pooled analysis of 11 case-control studies by Khoja et al. (7) found hysterectomy to be associated with a significantly reduced risk of ovarian cancer among women who had endometriosis, but to have no association among women who did not have endometriosis. Effect differences by history of endometriosis for other ovarian cancer risk factors are possible and should be evaluated, although to our knowledge only 1 study has done this.

Modugno et al. (8) considered the effect modification by endometriosis status and found no statistically significant

differences possibly because of a small sample size (177 ovarian cancer cases with endometriosis, 184 controls with endometriosis). Thus, we conducted a comprehensive study of endometriosis as an effect modifier of ovarian cancer risk factors using epidemiologic data from over 22,000 women in the Ovarian Cancer Association Consortium (OCAC), of whom more than 800 cases and 900 controls had endometriosis. Our analysis considers 10 well-established ovarian cancer risk factors, including body mass index (BMI), talcum powder (i.e., talc) use, family history of ovarian cancer, nonsteroidal anti-inflammatory drug (NSAID) use, breastfeeding, hormonal oral contraceptive use, parity, tubal ligation, menopausal hormone therapy (HT) use (estrogen-only therapy and estrogen-progestin therapy), and age at menarche. We hypothesized that the associations between these factors and ovarian cancer risk may be different among women with and without endometriosis.

MATERIALS AND METHODS

Study Population

Data from 9 population based case-control studies were included in this pooled analysis; 1 study was conducted in

Australia (9), 1 in Denmark (10), and the remaining in the United States (11–17). These studies are part of the OCAC, an international collaboration that collects and shares risk factor data for the purposes of increasing power for analyses of genetic and environmental exposures (<http://ocac.ccge.medschl.cam.ac.uk/>). Cases were women with pathologically confirmed high-grade serous, low-grade serous, mucinous, endometrioid, clear cell, and other invasive epithelial ovarian, fallopian tube, or primary peritoneal cancer diagnoses (hereafter referred to as ovarian cancer). Controls were women who had at least 1 ovary but had not been diagnosed with ovarian cancer on or before their reference date (i.e., date of interview at time of study enrollment). Details of each included study are summarized in Table 1. Overall, the study enrollment of cases and controls spanned from 1992 to 2010.

Across the 9 studies, 8,500 ovarian cancer cases and 13,592 control women self-reported whether they had a history of endometriosis and were thus included in the analysis (Table 1). Our study did have some overlap with the report by Modugno et al. (8) for participants ascertained from 1993 to 1999 for 2 OCAC studies: the Hawaii Ovarian Cancer Study (HAW) (approximately 58% of HAW participants; N = 1,047) and University of Southern California Study of Lifestyle and Women's Health (USC) (approximately 44% of USC participants, N = 1,996).

Institutional review board approval was obtained by the original studies, and all women had provided written informed consent.

Statistical Analysis

All data were self-reported using standardized in-person or phone interviews or self-completed questionnaires. The information collected reflected the time at each participant's reference date (i.e., date of diagnosis for cases, date of interview at the time of study enrollment for controls). We considered 10 risk factors whose associations with ovarian cancer have been well established in the literature. First-degree family history of ovarian cancer, tubal ligation, and NSAID use were evaluated as dichotomous yes/no or never/ever variables. Age at menarche was examined in age categories of <12, 12–14, and ≥15 years. Use of talc was categorized based on the area of application (i.e., genital or nongenital) with those who did not report using talc categorized as never users. Parity was grouped as nulliparous, 1, 2, and ≥3 births. BMI 1 year prior to the woman's reference date or 5 years prior for studies that did not ask for women's BMI 1 year prior was categorized as <18.5, 18.5–<25, 25–<30, and ≥30 kg/m². In addition, hormonal oral contraceptive use and breastfeeding were evaluated by total duration with categories of <1 (including never users), 1–<5, 5–<10, and ≥10 years for hormonal oral contraceptive use and never, <12, 12–<24, and ≥24 months for breastfeeding. We only considered postmenopausal HT use, hence we used age 50 as a proxy for age at menopause and only counted HT used at age 50 or later in our duration categories of never users (including those whose use was only before menopause [i.e. before age 50]), <5,

5–<10, and ≥10 years. This was done for estrogen-only therapy and estrogen-progestin therapy separately.

For most covariates and risk factors, the percentage of women missing data was minimal, ranging from 0.0% missing age to 4.4% missing family history of ovarian cancer (Supplementary Table 1, available online). The only exceptions were for NSAID use (31.4% missing) and talc use, which was not collected in the Danish study (the Malignant Ovarian Tumor Study [MAL]) and was missing in 5.0% of women in the Australian study (the Australian Ovarian Cancer Study [AUS]) and 41.4% in the US studies (Supplementary Table 1). Multiple imputation (*mice* package in R) was used to address data missingness, and 50 imputed datasets were generated. All variables in the dataset were initially considered for imputation, including those that were not used in the final models. The data were imputed separately for cases and controls and by geographic location (i.e., Australia, Denmark, the United States). The OCAC study was included as a predictor in the imputation for US studies.

All data were pooled, and logistic regression models were fit to assess the association between each factor and ovarian cancer risk overall and by histotype (where the numbers allowed) for women who had a history of endometriosis and women who did not, separately. None of the studies directly matched on the ovarian cancer risk factors evaluated although some did match on race/ethnicity (HAW and USC), neighborhood (USC), or age at reference date (AUS, the Connecticut Ovary Study [CON], the Diseases of the Ovary and Their Evaluation Study [DOV], HAW, the Hormones and Ovarian Cancer Prediction [HOP], MAL, the New England Case-Control Study of Ovarian Cancer [NEC], USC). Because studies have shown that unconditional logistic regression adjusting for matched factors improves precision when matching does not approximate unique matching pairs (e.g., matching on sibling) (18, 19), we adjusted for age (<40, in 5-year age groups to 74, ≥75 years), race/ethnicity (non-Hispanic White, Hispanic White, Black, Asian, and other), highest level of education attained (<high school, high school graduate, some college, and ≥college graduate) as a proxy for neighborhood/socioeconomic status as well as OCAC study. The impact of the other 9 factors on each factor's association with ovarian cancer risk was then evaluated, and only those that changed the association of interest by ≥10% were included in the final models. Sensitivity analyses adjusting on a priori confounders (i.e., those associated with both the exposure of interest and outcome and not mediators) were also conducted.

The models for breastfeeding were fit among parous women only (n = 17,919). In addition, since the study population included both pre and postmenopausal women, the models for estrogen-only therapy and estrogen-progestin therapy use were restricted to postmenopausal women (n = 14,661). Only exclusive estrogen-only therapy and estrogen-progestin therapy use was considered, hence postmenopausal women who used both types (n = 700) or an unknown type of HT (n = 149) were excluded from these analyses; those excluded from the analyses because of use of both estrogen-only therapy and estrogen-progestin therapy or an unknown type of HT (n = 849) had a similar proportion of endometriosis as those included in the analysis

TABLE 1

Characteristics of the Ovarian Cancer Association Consortium studies included in the analysis.

Site	Study name	Study location	Time period	Data collection method	No. of cases (% with endometriosis)	No. of controls (% with endometriosis)	Mean age at enrollment (SD)	
							Cases	Controls
AUS (9)	Australian Ovarian Cancer Study	Australia	2002–2005	Self-completed questionnaire	1,336 (8.2%)	1,491 (5.8%)	59.2 (10.7)	55.9 (12.5)
CON (11)	Connecticut Ovary Study	Connecticut, US	1999–2003	In-person interview	388 (12.4%)	551 (9.4%)	59.3 (10.9)	53.1 (10.4)
DOV (12)	Diseases of the Ovary and Their Evaluation Study	Washington, US	2002–2009	In-person interview	1,137 (11.3%)	1,828 (8.0%)	56.2 (8.9)	56.4 (9.3)
HAW (13)	Hawaii Ovarian Cancer Study	Hawaii, US	1993–2008	In-person interview	698 (10.7%)	1,103 (6.6%)	57.0 (12.7)	55.1 (14.6)
HOP (14)	Hormones and Ovarian Cancer Prediction	Western Pennsylvania, Northeast Ohio, Western New York, US	2003–2009	In-person interview	717 (8.5%)	1,802 (7.2%)	60.2 (12.3)	58.3 (12.4)
MAL (10)	Malignant Ovarian Tumor Study	Denmark	1994–1999	In-person or phone interview	504 (1.4%)	1,553 (1.0%)	58.8 (10.8)	57.1 (11.3)
NEC (15)	New England Case-Control Study of Ovarian Cancer	New Hampshire, Eastern Massachusetts, US	1992–2008	In-person interview	1,472 (9.9%)	2,100 (7.8%)	55.4 (11.1)	53.6 (12.5)
UCI (16)	University of California, Irvine Ovarian Cancer Study	Orange County and San Diego County, California, US	1995–2005	Self-completed questionnaire	348 (17.5%)	569 (12.7%)	57.8 (12.0)	54.2 (12.3)
USC (17)	University of Southern California Study of Lifestyle and Women’s Health	Los Angeles, California, US	1993–2010	In-person interview	1,900 (10.2%)	2,595 (6.7%)	57.3 (11.7)	54.4 (12.3)
Total:					8,500 (9.8%)	13,592 (6.7%)	57.5 (11.3)	55.5 (12.1)

AUS = Australian Ovarian Cancer Study; SD = standard deviation; HAW = Hawaii Ovarian Cancer Study; USC = University of Southern California Study of Lifestyle and Women’s Health; CON = Connecticut Ovary Study; DOV = Diseases of the Ovary and Their Evaluation Study; HOP = Hormones and Ovarian Cancer Prediction; MAL = Malignant Ovarian Tumor Study; NEC = New England Case-Control Study of Ovarian Cancer; UCI = University of California, Irvine Ovarian Cancer Study; USC = University of Southern California Study of Lifestyle and Women’s Health; No. = number; SD = standard deviation.

Phung. Ovarian cancer risk by endometriosis. Fertil Steril 2022.

($n = 13,812$) (9.4% and 7.5%, respectively). Because information on talc use was not collected in the study conducted in Denmark (MAL), the analyses for talc use were only based on the 8 OCAC studies in the United States and Australia.

Odds ratios (ORs) across the 50 imputed datasets were pooled using Rubin's rule to obtain a single point estimate (20). Confidence intervals (CIs) were calculated from pooled standard errors, which were derived from within and between imputation variances (20, 21). Likelihood ratio tests comparing models with and without interaction terms were conducted to generate P values for interactions to determine whether endometriosis statistically significantly modified any of the risk factor to ovarian cancer associations.

Among the 830 ovarian cancer cases with endometriosis, 329 were high-grade serous, 33 were low-grade serous, 32 were mucinous, 190 were endometrioid, 133 were clear cell, and the remaining 113 were other invasive, epithelial tumor types that were not classified as 1 of these 5 main histotypes, including mixed cell and Brenner tumors. As such, we had limited numbers to conduct meaningful histotype-specific analyses for most associations by endometriosis status, with the exception of the BMI 25–<30 kg/m² category.

All tests were two-sided, and P values that were ≤ 0.05 were considered statistically significant. The analyses were performed using R Studio version 1.3.1073.

RESULTS

The analyses included a total of 22,092 women across the 9 OCAC studies, the majority of whom were postmenopausal ($n = 14,661$). Among the 8,500 cases with ovarian cancer and 13,592 controls, 9.8% ($n = 830$) and 6.7% ($n = 914$) reported a history of endometriosis, respectively (Table 1). Overall, we did not find any statistically significant interactions between endometriosis and the 10 ovarian cancer risk factors considered in our analysis, although we did observe some qualitative differences by endometriosis status.

Although endometriosis did not statistically significantly interact with BMI (P -interaction = .51), among those with endometriosis, being overweight (i.e., BMI = 25–<30 kg/m²) was associated with a 27% increased risk of ovarian cancer compared with those having a normal weight (i.e., BMI = 18.5–<25 kg/m²) (OR = 1.27; 95% CI, 1.00–1.60), but showed no association for those without endometriosis (OR = 0.97; 95% CI, 0.91–1.05) (Table 2). An increased risk was also observed for those classified as obese (i.e., BMI = ≥ 30 kg/m²), although there was little difference in the ORs for those with endometriosis (OR = 1.21; 95% CI, 0.94–1.57) vs. those without (OR = 1.13; 95% CI, 1.04–1.22) (Table 2). When we considered histotype, we observed a difference in the association between being overweight and risk of ovarian cancer across histotypes when comparing women with and without endometriosis, although none of the interactions were statistically significant (Supplementary Fig. 1, available online).

Having a first-degree family history of ovarian cancer was associated with an increased risk regardless of endometriosis status; however, the increased risk appeared greater for women without endometriosis than women with endometriosis (OR = 2.20; 95% CI, 1.88–2.57 vs. OR = 1.58; 95% CI,

0.97–2.57, respectively; P -interaction = .20) (Table 2). Genital talc use was also positively associated with risk for women with and without endometriosis, although its magnitude seemed to be greater for women with than women without (OR = 1.38; 95% CI, 1.04–1.84 vs. OR = 1.12; 95% CI, 1.01–1.25, respectively; P -interaction = .65) (Table 2). A similar pattern was observed for longer menopausal estrogen-only therapy use; the increased risk appeared greater for women with vs. without endometriosis, particularly for those who used estrogen-only therapy for ≥ 10 years (OR = 1.88; 95% CI, 1.09–3.24 vs. OR = 1.42; 95% CI, 1.14–1.76, respectively, P -interaction = .96) (Table 3). On the other hand, use of estrogen-progestin therapy was inversely associated with ovarian cancer risk among women with endometriosis, but not associated with risk among women without endometriosis (for 5–<10 years: OR = 0.64; 95% CI, 0.38–1.07 vs. OR = 0.98; 95% CI, 0.84–1.14, respectively; P -interaction = .57) (Table 3).

For breastfeeding, hormonal oral contraceptive use, parity, tubal ligation, age at menarche, and NSAID use, the magnitudes of their associations with risk of ovarian cancer did not appear to differ by endometriosis status (Tables 2 and 3). Overall, none of the results changed when sensitivity analyses were conducted adjusting for a priori confounders (Supplementary Tables 2 and 3, available online).

DISCUSSION

Endometriosis is a common gynecologic condition and a well-established risk factor for ovarian cancer (22). Given the previous work showing hysterectomy's association with ovarian cancer risk to differ by endometriosis status (6, 7), we examined the relationships of 10 other ovarian cancer risk factors, including BMI, talc use, first-degree family history of ovarian cancer, NSAID use, breastfeeding, hormonal oral contraceptive use, parity, tubal ligation, HT use, and age at menarche. To our knowledge, this is the first analysis that considers all of these well-established ovarian cancer risk factors when examining endometriosis' potential interactions with regard to the ovarian cancer risk.

Although we did not observe a statistically significant interaction between endometriosis and BMI, the higher risk associated with being overweight among women with endometriosis is interesting because endometriosis is considered an inflammatory disease (23) and adiposity contributes to a proinflammatory state (24). This was seen across histotypes, and a possible explanation may be related to inflammation. Because inflammation plays a role in the development of many cancers, including ovarian cancer (25), the increased risk observed specifically among women with endometriosis is plausible because overweight women with endometriosis may have higher levels of inflammation. Both endometriotic foci (26, 27) and adipose tissues (28) produce proinflammatory cytokines, including TNF- α , IL-1, and IL-6. These proinflammatory cytokines have been shown to increase the risk of ovarian cancer as they promote the synthesis of prostaglandins (3), which in turns inhibits cell differentiation and apoptosis (29), and enhances invasion and angiogenesis (30). This would also be in line with our observation of a higher risk associated with genital talc use for women with endometriosis since

TABLE 2

Associations between family history and lifestyle factors and ovarian cancer risk by endometriosis status.

Risk Factor	Without Endometriosis (7,670 cases, 12,678 controls)				With Endometriosis (830 cases, 914 controls)				P-interaction ^c
	Cases ^a	Controls ^a	OR ^b	95% CI	Cases ^a	Controls ^a	OR ^b	95% CI	
BMI									.51
<18.5 kg/m ²	178	290	1.12	0.92–1.36	16	21	0.82	0.42–1.62	
18.5–<25 kg/m ²	3,554	6,267	1.00	—	403	475	1.00	—	
25–<30 kg/m ²	2,142	3,588	0.97	0.91–1.05	230	231	1.27	1.00–1.60	
≥30 kg/m ²	1,670	2,462	1.13	1.04–0.22	172	186	1.21	0.94–1.57	
				P-trend = .04 ^d				P-trend = .06 ^d	
Talc use ^e									.65
Never	2,172	4,137	1.00	—	220	323	1.00	—	
Nongenital use	1,391	1,909	0.76	0.49–1.19	162	140	0.83	0.39–1.77	
Genital use	827	1,304	1.12	1.01–1.25	79	106	1.38	1.04–1.84	
First-degree family history of ovarian cancer									.20
No	6,943	11,811	1.00	—	762	841	1.00	—	
Yes	397	309	2.20	1.88–2.57	41	30	1.58	0.97–2.57	
NSAID use									.50
Never	3,996	6,914	1.00	—	359	393	1.00	—	
Ever	1,130	2,007	0.90	0.78–1.04	169	196	0.85	0.63–1.13	

BMI = body mass index; CI = confidence interval; NSAID = nonsteroidal anti-inflammatory drug; OR = odds ratio.

^a Numbers may not sum to total because of missingness.^b Models were fit in 50 imputed datasets, pooled using Rubin's rule, and adjusted for age at reference date, race/ethnicity, education level, and Ovarian Cancer Association Consortium (OCAC) study.^c P value for interaction using a likelihood ratio test.^d P value for trend was calculated by fitting the categorical variable as an ordinal variable.^e Models were fit among participants in studies conducted in Australia and the United States only.Phung. Ovarian cancer risk by endometriosis. *Fertil Steril* 2022.

inflammation has been proposed as a possible biologic mechanism for talc's association with ovarian cancer (9).

Because endometriosis regresses after menopause and exposure to estrogen may reactivate endometriosis and stimulate carcinogenesis (31), we hypothesized that the association between estrogen-only therapy and ovarian cancer among women with endometriosis and women without endometriosis may differ. We did not observe endometriosis to statistically significantly interact with estrogen-only therapy, although longer use was associated with greater ovarian cancer risk among women with endometriosis, which is in line with estrogen's hypothesized role in endometriosis growth and ovarian cancer development. This difference in OR magnitude was not observed for short-term estrogen-only therapy use; however, this may be because estrogen-only therapy's effect on ovarian cancer has been shown to depend on the duration of use with substantial risk among long-term users (32). Interestingly, longer estrogen-progestin therapy use showed an inverse association for women with endometriosis, but there was no association with ovarian cancer risk for women without endometriosis. Some studies have shown that including a progestin component to an estrogen-only therapy regimen (i.e., estrogen-progestin therapy) may ameliorate some of the carcinogenic effects of estrogen when it comes to ovarian cancer risk (33, 34), and progestin therapy is often used to treat endometriosis (35). Information regarding the progestin included in the HT as well as endometriosis treatments would be relevant, although this information was unavailable.

A first-degree family history of ovarian cancer was associated with an increased ovarian cancer risk among women with

and without endometriosis, although the magnitude of the association was greater for those who did not have endometriosis. It is unclear to us why this positive association may be greater for those without endometriosis. Studies have shown that high-grade serous, which is the most common histotype, is strongly associated with pathogenic variants in *BRCA1* and *BRCA2*, and this histotype is not associated with endometriosis (36). Endometrioid and clear cell ovarian cancer have also been shown to be associated with pathogenic variants in Lynch syndrome genes, and both histotypes are more common among women with endometriosis (36). Knowing the prevalence of these variants in women with and without endometriosis would be relevant, but to our knowledge, this has not been examined. However, at the same time, we acknowledge that the observed results may simply be due to chance given the small number of women with endometriosis and a family history of ovarian cancer.

A limitation of our study is that the information on endometriosis was based on self-report, and as such there could be misclassification. This misclassification would make the associations more similar when comparing women with and without endometriosis. However, it has been shown that self-reported endometriosis is reasonably accurate when compared with diagnosed endometriosis with at least 70% accuracy (37). An important strength of our study is our large sample size; we included over 22,000 women from various geographic regions, and of them, over 1,700 women had endometriosis. The only other study, to our knowledge, that has examined endometriosis' interactive effects with other ovarian cancer risk factors is the study by Modugno et al. (8), which included <400 women who self-reported a history

TABLE 3

Associations between hormonal and reproductive risk factors and ovarian cancer risk by endometriosis status.

Risk Factor	Without endometriosis (7,670 cases, 12,678 controls)				With endometriosis (830 cases, 914 controls)				P-interaction ^c	Risk factors adjusted
	Cases ^a	Controls ^a	OR ^b	95% CI	Cases ^a	Controls ^a	OR ^b	95% CI		
Breastfeeding ^d (mo)									.91	Parity
Never	2,226	3,021	1.00	—	196	201	1.00	—		
<12	2,176	4,184	0.81	0.74–0.88	201	279	0.70	0.53–0.94		
12–<24	878	1,804	0.78	0.71–0.87	73	110	0.67	0.46–0.99		
≥24	547	1,510	0.60	0.53–0.68	42	78	0.60	0.38–0.96		
				P-trend < .001 ^e				P-trend = .009 ^e		
Duration of hormonal oral contraceptive use (y)									.91	
Never or <1	4,363	5,395	1.00	—	382	309	1.00	—		
1–<5	1,629	2,987	0.67	0.62–0.73	212	265	0.63	0.49–0.80		
5–<10	936	2,114	0.54	0.49–0.59	131	174	0.57	0.42–0.76		
≥10	714	2,163	0.38	0.35–0.42	103	162	0.47	0.34–0.64		
				P-trend < .001 ^e				P-trend < .001 ^e		
Parity									.40	Breastfeeding and tubal ligation
0 births	1,761	1,886	1.00	—	310	211	1.00	—		
1 birth	1,042	1,652	0.75	0.67–0.84	147	165	0.80	0.57–1.13		
2 births	2,229	4,236	0.63	0.57–0.70	216	279	0.75	0.54–1.02		
≥3 births	2,635	4,902	0.58	0.52–0.64	157	259	0.61	0.43–0.88		
				P-trend < .001 ^e				P-trend = .009 ^e		
Tubal ligation									.28	Parity and breastfeeding
No	6,444	9,666	1.00	—	714	667	1.00	—		
Yes	1,195	2,749	0.67	0.61–0.72	111	207	0.62	0.47–0.82		
Duration of estrogen-only therapy use ^f (y)									.96	
Never	4,274	6,367	1.00	—	372	425	1.00	—		
<5	425	699	0.97	0.83–1.13	60	69	0.83	0.52–1.32		
5–<10	218	268	1.17	0.95–1.45	36	34	1.23	0.71–2.12		
≥10	351	373	1.42	1.14–1.76	45	34	1.88	1.09–3.24		
				P-trend = .002 ^e				P-trend = .05 ^e		
Duration of estrogen-progestin therapy use ^f (y)									.57	Hormonal oral contraceptive use
Never	4,002	5,528	1.00	—	392	402	1.00	—		
<5	612	1,155	0.76	0.67–0.86	68	86	0.70	0.47–1.07		
5–<10	381	576	0.98	0.84–1.14	36	51	0.64	0.38–1.07		
≥10	255	414	0.93	0.76–1.12	17	22	0.68	0.33–1.39		
				P-trend = .06 ^e				P-trend = .03 ^e		
Age at menarche (y)									.76	
<12	1,499	2,509	0.96	0.89–1.03	212	225	1.04	0.83–1.30		
12–14	5,140	8,362	1.00	—	544	594	1.00	—		
≥15	981	1,731	0.89	0.81–0.97	73	90	0.89	0.63–1.25		
				P-trend = .35 ^e				P-trend = .46 ^e		

CI=confidence interval; OR=odds ratio.

^a Numbers may not sum to total because of missingness.^b Models were fit in 50 imputed datasets, pooled using Rubin's rule, and adjusted for age at reference date, race/ethnicity, education level, Ovarian Cancer Association Consortium (OCAC) study, and other risk factors indicated in the "Risk factors adjusted" column.^c P value for interaction with endometriosis using a likelihood ratio test.^d Models were restricted to parous women only.^e P value for trend was calculated by fitting the categorical variable as an ordinal variable.^f Models were restricted to postmenopausal women only, excluding those who had ever used both estrogen-only therapy and estrogen-progestin therapy and those who used an unknown hormone therapy type.

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of endometriosis. Similar to the study by Modugno et al., we did not find any statistically significant interactions with hormonal oral contraceptive use, parity, and tubal ligation as well as observed ovarian cancer risk reductions of equal magnitude regardless of endometriosis status for all 3 factors. Although the type of hormonal oral contraception used likely varies between women with and without endometriosis, this information was unavailable.

Despite our large sample size, we had limited numbers to examine most associations by endometriosis status and histotype, and some risk factors have been shown to have histotype-specific effects. For example, studies have shown that BMI is associated with increased risk of endometrioid and low-grade serous ovarian cancer (38); estrogen-only therapy use is associated with increased risk of serous and endometrioid ovarian cancer (32); and genital talc use is associated with increased risk of serous, endometrioid, and clear cell ovarian cancer (39). It is possible that the differential associations that we observed by endometriosis status could partly be attributable to the histotype. However, when we examined the association between overweight and ovarian cancer by endometriosis status, we observed higher ORs among women with endometriosis regardless of the histotype.

In conclusion, our study is the first to examine endometriosis' interactive effects with 10 well-established ovarian cancer risk factors on risk of ovarian cancer. Most risk factors showed similar associations among women with and without endometriosis, and none of the interactions that we evaluated were statistically significant. However, there was some suggestion that the associations for BMI, genital talc use, and HT use may differ between women with and without endometriosis, which may be worth further exploring. A better understanding of the mechanisms underlying these findings is still needed, but regardless, our study provides some insight into the etiology of this complex disease.

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SUPPLEMENTARY TABLE 1. Characteristics of participants in the analysis by endometriosis status

	Without Endometriosis		With Endometriosis	
Characteristic	Cases N (%)^a	Controls N (%)^a	Cases N (%)^a	Controls N (%)^a
Age ^b	57.9 (11.4)	55.7 (12.2)	54.0 (9.72)	53.8 (10.3)
Race/ethnicity				
Non-Hispanic White	6406 (83.5%)	10913 (86.1%)	690 (83.1%)	802 (87.7%)
Hispanic White	343 (4.5%)	437 (3.4%)	21 (2.5%)	21 (2.3%)
Black	168 (2.2%)	242 (1.9%)	16 (1.9%)	15 (1.6%)
Asian	449 (5.9%)	561 (4.4%)	67 (8.1%)	44 (4.8%)
Other	279 (3.6%)	495 (3.9%)	32 (3.9%)	30 (3.3%)
Missing	25 (0.3%)	30 (0.2%)	4 (0.5%)	2 (0.2%)
Education level				
Less than high school	1352 (17.6%)	2112 (16.7%)	49 (5.9%)	53 (5.8%)
High school graduate	1845 (24.1%)	2766 (21.8%)	140 (16.9%)	182 (19.9%)
Some college	2048 (26.7%)	3213 (25.3%)	255 (30.7%)	260 (28.4%)
College graduate or above	2167 (28.3%)	4166 (32.9%)	355 (42.8%)	364 (39.8%)
Missing	258 (3.4%)	421 (3.3%)	31 (3.7%)	55 (6.0%)
Body mass index				
<18.5 kg/m ²	178 (2.3%)	290 (2.3%)	16 (1.9%)	21 (2.3%)
18.5-<25 kg/m ²	3554 (46.3%)	6267 (49.4%)	403 (48.6%)	475 (52.0%)
25-<30 kg/m ²	2142 (27.9%)	3588 (28.3%)	230 (27.7%)	231 (25.3%)
30+ kg/m ²	1670 (21.8%)	2462 (19.4%)	172 (20.7%)	186 (20.4%)
Missing	126 (1.6%)	71 (0.6%)	9 (1.1%)	1 (0.1%)
Breastfeeding				
Never	3987 (52.0%)	4907 (38.7%)	506 (61.0%)	412 (45.1%)
<12 months	2176 (28.4%)	4184 (33.0%)	201 (24.2%)	279 (30.5%)
12-<24 months	878 (11.4%)	1804 (14.2%)	73 (8.8%)	110 (12.0%)
24+ months	547 (7.1%)	1510 (11.9%)	42 (5.1%)	78 (8.5%)
Missing	82 (1.1%)	273 (2.2%)	8 (1.0%)	35 (3.8%)
Hormonal oral contraceptive use				
<1 year	4363 (56.9%)	5395 (42.6%)	382 (46.0%)	309 (33.8%)
1-<5 years	1629 (21.2%)	2987 (23.6%)	212 (25.5%)	265 (29.0%)
5-<10 years	936 (12.2%)	2114 (16.7%)	131 (15.8%)	174 (19.0%)
10+ years	714 (9.3%)	2163 (17.1%)	103 (12.4%)	162 (17.7%)
Missing	28 (0.4%)	19 (0.1%)	2 (0.2%)	4 (0.4%)
First-degree family history of ovarian cancer				
No	6943 (90.5%)	11811 (93.2%)	762 (91.8%)	841 (92.0%)
Yes	397 (5.2%)	309 (2.4%)	41 (4.9%)	30 (3.3%)
Missing	330 (4.3%)	558 (4.4%)	27 (3.3%)	43 (4.7%)
Parity				
0 births	1761 (23.0%)	1886 (14.9%)	310 (37.3%)	211 (23.1%)

1 birth	1042 (13.6%)	1652 (13.0%)	147 (17.7%)	165 (18.1%)
2 births	2229 (29.1%)	4236 (33.4%)	216 (26.0%)	279 (30.5%)
3+ births	2635 (34.4%)	4902 (38.7%)	157 (18.9%)	259 (28.3%)
Missing	3 (0.0%)	2 (0.0%)	0 (0%)	0 (0%)
Tubal ligation				
No	6444 (84.0%)	9666 (76.2%)	714 (86.0%)	667 (73.0%)
Yes	1195 (15.6%)	2749 (21.7%)	111 (13.4%)	207 (22.6%)
Missing	31 (0.4%)	263 (2.1%)	5 (0.6%)	40 (4.4%)
Estrogen-only therapy use ^c				
Never	4274 (77.4%)	6367 (79.4%)	372 (69.7%)	425 (73.4%)
<5 years	425 (7.7%)	699 (8.7%)	60 (11.2%)	69 (11.9%)
5-<10 years	218 (3.9%)	268 (3.3%)	36 (6.7%)	34 (5.9%)
10+ years	351 (6.4%)	373 (4.6%)	45 (8.4%)	34 (5.9%)
Missing	257 (4.7%)	316 (3.9%)	21 (3.9%)	17 (2.9%)
Estrogen-progestin therapy use ^c				
Never use	4002 (72.4%)	5528 (68.9%)	392 (73.4%)	402 (69.4%)
<5 years	612 (11.1%)	1155 (14.4%)	68 (12.7%)	86 (14.9%)
5-<10 years	381 (6.9%)	576 (7.2%)	36 (6.7%)	51 (8.8%)
10+ years	255 (4.6%)	414 (5.2%)	17 (3.2%)	22 (3.8%)
Missing	275 (5.0%)	350 (4.4%)	21 (3.9%)	18 (3.1%)
NSAID use				
Never	3996 (52.1%)	6914 (54.5%)	359 (43.3%)	393 (43.0%)
Ever	1130 (14.7%)	2007 (15.8%)	169 (20.4%)	196 (21.4%)
Missing	2544 (33.2%)	3757 (29.6%)	302 (36.4%)	325 (35.6%)
Age at menarche				
<12 years	1499 (19.5%)	2509 (19.8%)	212 (25.5%)	225 (24.6%)
12-14 years	5140 (67.0%)	8362 (66.0%)	544 (65.5%)	594 (65.0%)
15+ years	981 (12.8%)	1731 (13.7%)	73 (8.8%)	90 (9.8%)
Missing	50 (0.7%)	76 (0.6%)	1 (0.1%)	5 (0.5%)
Talc use				
Never	2172 (28.3%)	4137 (32.6%)	220 (26.5%)	323 (35.3%)
Non-genital use	1391 (18.1%)	1909 (15.1%)	162 (19.5%)	140 (15.3%)
Genital use	827 (10.8%)	1304 (10.3%)	79 (9.5%)	106 (11.6%)
Missing	3280 (42.8%)	5328 (42.0%)	369 (44.5%)	345 (37.7%)
Total:	7670 (100%)	12678 (100%)	830 (100%)	914 (100%)

Note. The missing data for each characteristic were imputed in the analysis.

Abbreviations: NSAID=nonsteroidal anti-inflammatory drug.

^a Number of cases/controls (% of cases/controls).

^b Mean (standard deviation).

^c Among postmenopausal women only.

SUPPLEMENTARY TABLE 2. Associations between family history and lifestyle factors and ovarian cancer risk by endometriosis status comparing main analysis to sensitivity analysis

	Main Analysis (adjusted for confounders using 10% criterion)				Sensitivity Analysis (adjusted for <i>a priori</i> confounders)			
	Without Endometriosis	With Endometriosis			Without Endometriosis	With Endometriosis		
	OR (95% CI) ^a	OR (95% CI) ^a	p-interaction ^b	Risk Factors Adjusted	OR (95% CI) ^a	OR (95% CI) ^a	p-interaction ^b	Risk Factors Adjusted
Body mass index			0.51				0.51	Menopausal status
<18.5 kg/m ²	1.17 (0.95-1.44)	0.82 (0.42-1.62)			1.16 (0.94-1.43)	0.84 (0.42-1.68)		
18.5-<25 kg/m ²	1.0	1.0			1.0	1.0		
25-<30 kg/m ²	0.98 (0.91-1.05)	1.26 (0.99-1.59)			0.97 (0.90-1.05)	1.24 (0.97-1.58)		
30+ kg/m ²	1.14 (1.05-1.24)	1.21 (0.94-1.57)			1.14 (1.05-1.23)	1.20 (0.92-1.57)		
First-degree family history of ovarian cancer			0.18				0.18	
No	1.0	1.0			1.0	1.0		
Yes	2.18 (1.85-2.57)	1.58 (0.97-2.57)			2.18 (1.85-2.57)	1.58 (0.97-2.57)		
NSAID use			0.50				0.50	
Never	1.0	1.0			1.0	1.0		
Ever	0.90 (0.78-1.04)	0.85 (0.63-1.13)			0.90 (0.78-1.04)	0.85 (0.63-1.13)		
Talc use			0.65				0.65	
Never	1.0	1.0			1.0	1.0		
Genital use	1.12 (1.01-1.25)	1.38 (1.04-1.84)			1.12 (1.01-1.25)	1.38 (1.04-1.84)		
Non-genital use	0.76 (0.49-1.19)	0.83 (0.39-1.77)			0.76 (0.49-1.19)	0.83 (0.39-1.77)		

Note. The above analyses are based on 8 Ovarian Cancer Association Consortium (OCAC) studies only. We cannot access the Malignant Ovarian Tumor Study's (MAL's) data at this time due to the European Union's General Data Protection Regulation.

Abbreviations: CI=confidence interval; NSAID=nonsteroidal anti-inflammatory drug; OR=odds ratio.

^a Models were fit in 50 imputed datasets, pooled using Rubin's rule, and adjusted for age, race/ethnicity, education level, OCAC study, and other risk factors indicated in the "Risk Factors Adjusted" column.

^b P-value for interaction with endometriosis using a likelihood ratio test.

SUPPLEMENTARY TABLE 3. Associations between hormonal and reproductive risk factors and ovarian cancer risk by endometriosis status comparing main analysis to sensitivity analysis

	Main Analysis (adjusted for confounders using 10% criterion)				Sensitivity Analysis (adjusted for <i>a priori</i> confounders)			
	Without Endometriosis	With Endometriosis			Without Endometriosis	With Endometriosis		
	OR (95% CI) ^a	OR (95% CI) ^a	p-interaction ^b	Risk Factors Adjusted	OR (95% CI) ^a	OR (95% CI) ^a	p-interaction ^b	Risk Factors Adjusted
Breastfeeding ^c			0.91	Parity			0.91	Parity, hormonal oral contraceptive use
Never	1.0	1.0			1.0	1.0		
<12 months	0.81 (0.75-0.88)	0.70 (0.53-0.94)			0.82 (0.75-0.89)	0.69 (0.51-0.92)		
12-<24 months	0.78 (0.70-0.87)	0.67 (0.45-0.99)			0.78 (0.69-0.87)	0.64 (0.43-0.95)		
24+ months	0.59 (0.52-0.67)	0.59 (0.37-0.95)			0.57 (0.50-0.65)	0.55 (0.34-0.89)		
Hormonal oral contraceptive use			0.22				0.19	Age at menarche, parity, breastfeeding
Never or <1 year	1.0	1.0			1.0	1.0		
1-<5 years	0.67 (0.62-0.73)	0.63 (0.49-0.81)			0.71 (0.66-0.77)	0.65 (0.50-0.84)		
5-<10 years	0.54 (0.49-0.59)	0.56 (0.42-0.75)			0.55 (0.50-0.61)	0.56 (0.41-0.75)		
10+ years	0.38 (0.35-0.43)	0.47 (0.34-0.63)			0.37 (0.34-0.41)	0.45 (0.33-0.62)		
Parity			0.36	Breastfeeding, tubal ligation			0.22	Hormonal oral contraceptive use
0 births	1.0	1.0			1.0	1.0		
1 birth	0.75 (0.66-0.84)	0.80 (0.57-1.12)			0.66 (0.59-0.74)	0.64 (0.48-0.86)		
2 births	0.65 (0.58-0.72)	0.74 (0.54-1.02)			0.53 (0.48-0.58)	0.53 (0.41-0.69)		
3+ births	0.59 (0.52-0.65)	0.61 (0.43-0.88)			0.41 (0.38-0.45)	0.39 (0.29-0.52)		
Tubal ligation			0.22	Parity, breastfeeding			0.18	Parity, hormonal oral contraceptive use
No	1.0	1.0			1.0	1.0		
Yes	0.66 (0.61-0.72)	0.60 (0.46-0.80)			0.70 (0.65-0.77)	0.64 (0.49-0.85)		
Age at menarche			0.66				0.66	
<12 years	0.94 (0.87-1.02)	1.05 (0.83-1.32)			0.94 (0.87-1.02)	1.05 (0.83-1.32)		
12-14 years	1.0	1.0			1.0	1.0		
15+ years	0.91 (0.82-1.00)	0.91 (0.65-1.27)			0.91 (0.82-1.00)	0.91 (0.65-1.27)		

	Main Analysis (adjusted for confounders using 10% criterion)				Sensitivity Analysis (adjusted for <i>a priori</i> confounders)			
	Without Endometriosis	With Endometriosis			Without Endometriosis	With Endometriosis		
	OR (95% CI) ^a	OR (95% CI) ^a	p-interaction ^b	Risk Factors Adjusted	OR (95% CI) ^a	OR (95% CI) ^a	p-interaction ^b	Risk Factors Adjusted
Estrogen-only therapy use ^d			0.94				0.91	Hormonal oral contraceptive use
Never	1.0	1.0			1.0	1.0		
<5 years	1.05 (0.90-1.23)	0.85 (0.53-1.36)			1.08 (0.92-1.26)	0.86 (0.54-1.39)		
5-<10 years	1.20 (0.97-1.49)	1.23 (0.71-2.13)			1.25 (1.00-1.55)	1.27 (0.73-2.21)		
10+ years	1.48 (1.24-1.77)	1.95 (1.12-3.37)			1.51 (1.26-1.80)	2.09 (1.20-3.64)		
Estrogen-progestin therapy use ^d			0.67	Hormonal oral contraceptive use duration			0.67	Hormonal oral contraceptive use
Never	1.0	1.0			1.0	1.0		
<5 years	0.74 (0.65-0.84)	0.71 (0.47-1.08)			0.74 (0.65-0.84)	0.71 (0.47-1.08)		
5-<10 years	0.92 (0.78-1.07)	0.64 (0.38-1.08)			0.92 (0.78-1.07)	0.64 (0.38-1.08)		
10+ years	0.89 (0.74-1.08)	0.69 (0.33-1.41)			0.89 (0.74-1.08)	0.69 (0.33-1.41)		

Note. The above analyses are based on 8 Ovarian Cancer Association Consortium (OCAC) studies only. We cannot access the Malignant Ovarian Tumor Study's (MAL's) data at this time due to the European Union's General Data Protection Regulation.

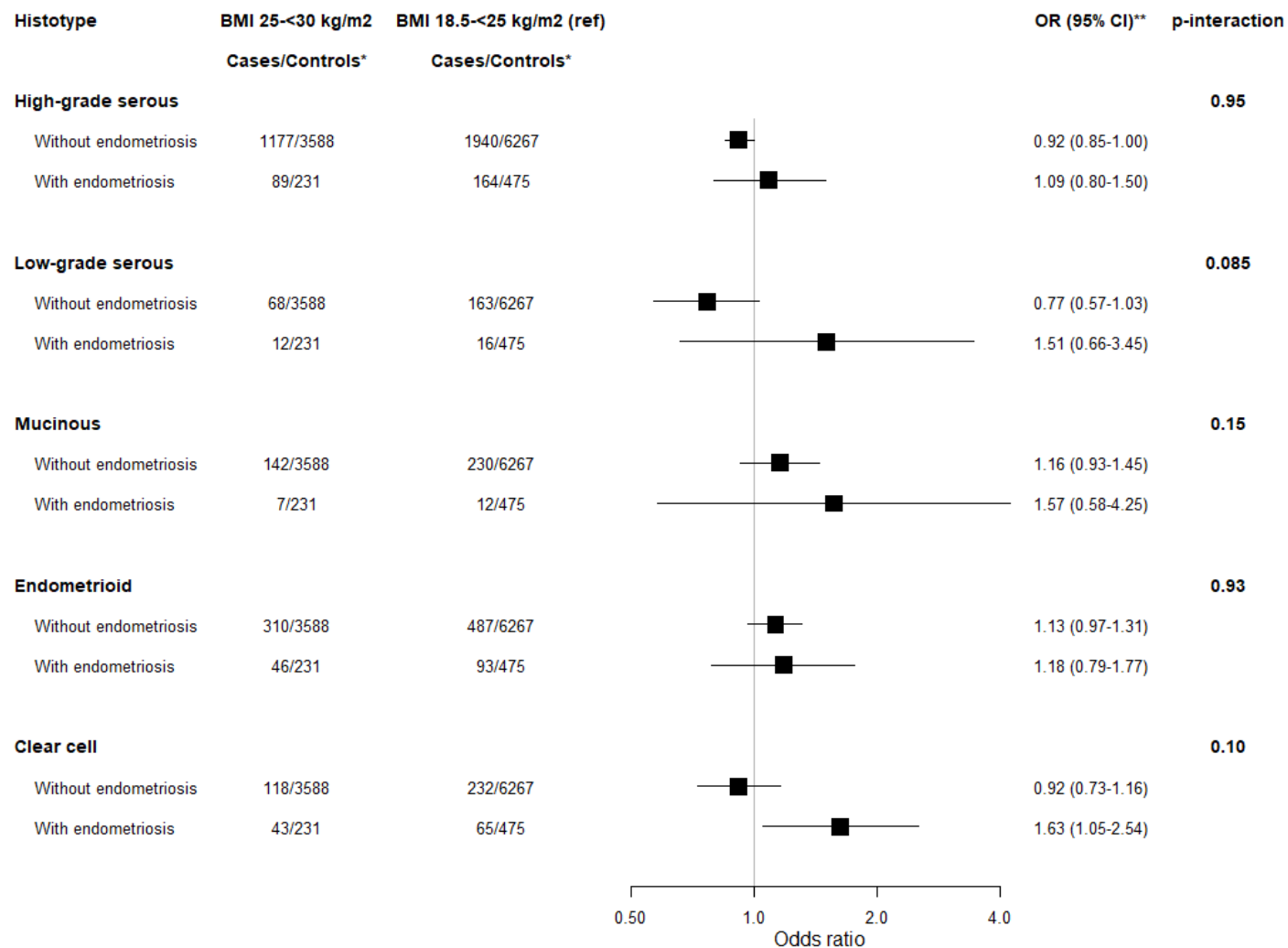
Abbreviations: CI=confidence interval; OR=odds ratio.

^a Models were fit in 50 imputed datasets, pooled using Rubin's rule, and adjusted for age at reference date, race/ethnicity, education level, OCAC study, and other risk factors indicated in the "Risk Factors Adjusted" column.

^b P-value for interaction with endometriosis using a likelihood ratio test.

^c Models were restricted to parous women only.

^d Models were restricted to postmenopausal women only, excluding those who had ever used both estrogen-only therapy and estrogen-progestin therapy and those who used an unknown hormone therapy type.



SUPPLEMENTARY FIGURE 1. Odds ratios (ORs) and 95% confidence intervals (CIs) for the association between body mass index (25-<30 kg/m² compared to 18.5-<25 kg/m²) and risk of ovarian cancer for women with and without endometriosis by histotype.

* Numbers may not sum to total due to missingness.

** Models were fit in 50 imputed datasets, pooled using Rubin's rule, and adjusted for age at reference date, race/ethnicity, education level, and Ovarian Cancer Association Consortium (OCAC) study.